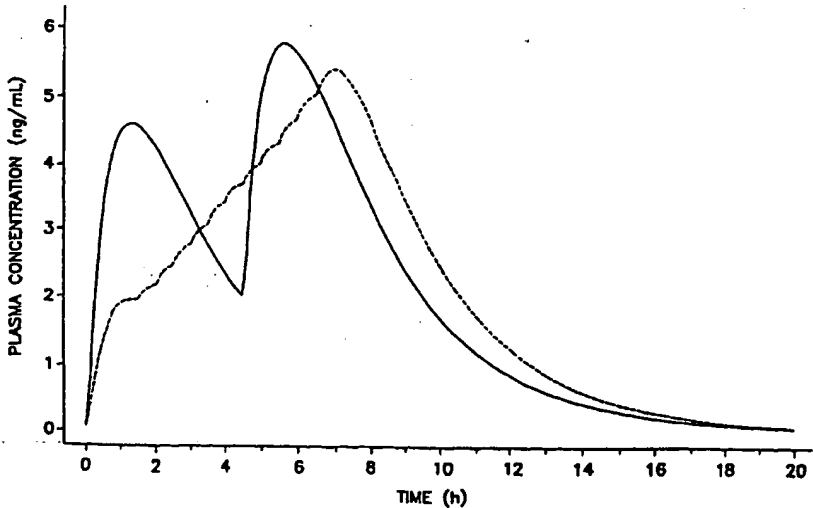




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/16599 <b>(22) International Filing Date:</b> 16 September 1997 (16.09.97)  <b>(30) Priority Data:</b> 60/028,726 30 September 1996 (30.09.96) US 60/030,514 12 November 1996 (12.11.96) US 60/044,121 22 April 1997 (22.04.97) US  <b>(71) Applicant:</b> ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).  <b>(72) Inventors:</b> GUPTA, Suneel, K.; 1331 Elsona Drive, Sunnyvale, CA 94087 (US). GUINTA, Diane, R.; 3164 Manchester Court, Palo Alto, CA 94303 (US). CHRISTOPHER, Carol, A.; 2638 Belmont Canyon Road, Belmont, CA 94002 (US). SAKS, Samuel, R.; 2404 Hillside Drive, Burlingame, CA 94010 (US).  <b>(74) Agents:</b> SABATINE, Paul, L. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> DOSAGE FORM AND METHOD FOR ADMINISTERING DRUG    <b>(57) Abstract</b>  A dosage form and a method are disclosed and claimed for administering a drug in a sustained and constantly ascending rate per unit time to provide an intended therapeutic effect while concomitantly lessening the development of unwanted effects.		

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1           **DOSAGE FORM AND METHOD FOR ADMINISTERING DRUG**

2  
3           **FIELD OF THE INVENTION**

4  
5           This invention pertains to both a novel dosage form and to a novel  
6 method for administering a drug for producing a therapeutic effect. The  
7 invention concerns more specifically a dosage form that administers at a  
8 sustained and continuously ascending rate a drug to produce a given therapy,  
9 and more specifically a method for producing a therapeutic effect by  
10 administering over a predetermined period at a sustained and continuously  
11 ascending rate a drug to produce a given therapy. The invention relates also  
12 to a dosage form and to a method for achieving a therapeutic effect by  
13 administering an initial dose of drug followed by a sustained and increasing  
14 dose of drug over an extended time.

15  
16           **BACKGROUND OF THE INVENTION**

17  
18           For a long time, pharmacy and medicine in every society used  
19 drugs that produce effects on pain, mood, thought, feeling, behavior,  
20 and psychological personality. These drugs are represented by opioids,  
21 barbiturates, hypnotics, central nervous system stimulants, central nervous  
22 system depressants, psychostimulants, alcohols, cannabinoids, and  
23 catecholamines. In present medicine, one class of these drugs has become  
24 the standard invention for the management of Attention-Deficit Disorder,  
25 that is, the central nervous system stimulants. While this invention presents  
26 central nervous system drugs in greater detail, it is understood the invention  
27 is generic and embraces drugs broadly administered using the dosage forms  
28 and the method of the invention.

29           The benefits perceived by parents, teachers, physicians,  
30 psychologists, social workers, and clinicians are dramatic for central nervous  
31 system drugs, and this has resulted in the widespread and acceptable use

1 of central nervous system medication to treat Attention-Deficit Disorder.

2 In 1994, the latest period for collecting data, it was observed that about two  
3 percent of the school-aged female population and about six percent of the  
4 school-aged male population, for a total of about two million patients, were  
5 administered the medication for Attention-Deficit Disorder.

6 Prior to the advent of this invention, the dosage form and the method  
7 for administering a drug, for example, a central nervous system acting drug,  
8 consisted in using a standard pharmaceutical dosage form. For example,  
9 one prior art dosage form and method for administering a drug, such as the  
10 central nervous system drug methylphenidate, consists in using an immediate  
11 release tablet containing the drug. This immediate release form delivers the  
12 drug by instant dumping of the drug and this produces uneven blood levels  
13 characterized by peaks and valleys. For an immediate release form  
14 containing methylphenidate which is characterized by a rapid onset and a  
15 short half-life to produce the intended therapy, multiple doses are needed  
16 each day that can result in swings in behavior and in attention as the  
17 medication loses its therapeutic effect. This dosage form does not provide  
18 the needed therapy over an extended time.

19 Another prior art dosage form for dispensing a drug is the sustained-  
20 release dosage form. A drug dispensed from a prior art sustained-release  
21 dosage form may ascend initially but not over the entire dosing interval, and it  
22 actually may decline over time. That is, these sustained-release dosage forms  
23 dispense a drug in a nonascending profile over time, as they do not provide a  
24 continuously increasing release rate per hour throughout the extended dosing  
25 period. This dosage form, additionally, may not provide the required duration  
26 of therapy and the appropriate blood pattern. For drugs that act on the central  
27 nervous system, like methylphenidate, dispensed from a sustained-release  
28 nonascending dosage form, the patient often develops an acute tolerance to  
29 the drug manifested by a shortened duration and a decrease in the intensity of  
30 the therapeutic effect needed for acceptable therapy. The prior sustained-

1 release delivery is also devoid of means that compensate for its shortcomings  
2 inherent therein.

3 The above presentation teaches that a critical need exists for a novel  
4 dosage form and for a novel method for administering a drug that overcomes  
5 the shortcomings known to the prior art. This long-felt need exists for a dosage  
6 form and for a method for (1) administering the drug at a sustained-increasing  
7 rate that simultaneously reduces or eliminates the frequency of daily dosing;  
8 for (2) a dosage form and a method for administering the drug in a sustained-  
9 compensating dose to substantially compensate for acute tolerance to the drug  
10 thereby maintaining a preselected clinical response; for (3) a dosage form that  
11 administers the drug in a sustained-ascending profile clinically indicated for the  
12 management of Attention-Deficit Disorders; and, for (4) a dosage form and a  
13 method for administering the drug initially and in a sustained-ascending profile  
14 throughout the entire school day.

15

16

#### OBJECTS OF THE INVENTION

17

18 Accordingly, in view of the above presentation, it is an immediate  
19 object of this invention to make available a dosage form that overcomes the  
20 shortcomings known in the prior art.

21 Another object of the invention is to provide a novel and unique dosage  
22 form that delivers a drug in a controlled increasing dose to a patient over time.

23 Another object of the invention is to provide a dosage form that  
24 administers a dose of drug to maintain the therapeutic effect of the drug in a  
25 patient that acquires tolerance to the drug by delivering the drug in a controlled-  
26 increasing dose over time to maintain the therapeutic effect, while  
27 concomitantly substantially avoiding the development of acute tolerance.

28 Another object of the invention is to make available a dosage form that  
29 delivers a dose of drug that essentially avoids or lessens the development of  
30 acquired tolerance in a patient administered a drug that leads to acute

1 tolerance by the dosage form administering the drug in a sustained and  
2 increasing dose over time.

3 Another object of the invention is to provide a dosage form for  
4 administering a central nervous system drug that overcomes the shortcomings  
5 known to the prior art.

6 Another object of the invention is to provide an improvement in a dosage  
7 form, wherein the improvement comprises the dosage form administering the  
8 drug in a sustained and constantly ascending profile over time for treating  
9 Attention-Deficit Disorder.

10 Another object of the invention is to provide a pharmacological  
11 composition as a solid dosage form comprising 1 mg to 500 mg of drug in  
12 admixture with a pharmaceutically acceptable carrier that is released in a  
13 sustained release and increasing dose for use in the treatment of psychological  
14 personalities.

15 Another object of the invention is to provide a dosage form for increasing  
16 the administration of a central nervous system acting drug per hour throughout  
17 a school day of 4 to 8-1/2 hours.

18 Another object of the invention is to provide a dosage form for  
19 administering a drug possessing central nervous system therapy in a  
20 sustained-increasing rate and at a minimum dose per day.

21 Another object of the invention is to provide a dosage form for  
22 administering a central nervous system acting drug in a drug delivery  
23 pattern that compensates for acquired tolerance associated with the drug.

24 Another object of the invention is to provide a dosage form that  
25 administers a drug for treating Attention-Deficit Disorder that comprises  
26 administering orally to a human diagnosed as having the disorder the drug in a  
27 sustained and increasing dose of 100 ng to 375 mg over 16 hours for treating  
28 the disorder in a human.

29 Another object of this invention is to provide a novel and unique method  
30 for maintaining the therapeutic effect of a drug in a patient that acquires  
31 tolerance to the drug, wherein the method comprises administering a dosage

1 form to the patient that delivers the drug in a controlled increasing dose over an  
2 extended time to maintain the therapeutic effect, while concomitantly  
3 substantially avoiding the development of acute tolerance in the patient.

4 Another object of the invention is to make available a method for  
5 essentially avoiding or lessening the development of the acquired tolerance  
6 in a patient administered a drug that develops acute tolerance in the patient,  
7 wherein the method comprises administering the drug in a sustained and  
8 increasing dose over time to produce the intended effect.

9 Another object of the invention is to provide an improvement in a method  
10 for administering a drug, wherein the improvement comprises administering the  
11 drug in a sustained and constantly ascending profile over an extended time for  
12 treating Attention-Deficit Disorder.

13 Another object of the invention is to provide a method for administering a  
14 central nervous system acting drug in a continuously increasing release rate  
15 per hour throughout a school day of 4 to 8-1/2 hours.

16 Another object of the invention is to provide a novel method to  
17 compensate for acute tolerance development associated with a drug  
18 possessing the ability to produce tolerance in a patient, by administering the  
19 drug orally in a sustained-ascending dose to substantially lessen the unwanted  
20 effects of acute tolerance.

21 Another object of the invention is to provide an improvement in a method  
22 for administering a drug possessing central nervous system stimulant therapy,  
23 wherein the improvement comprises administering the drug in a sustained and  
24 ascending pattern over an extended time for treating Attention-Deficit Disorders  
25 and additionally provides therapeutic compensation for acquired tolerance  
26 associated with the drug.

27 Another object of the invention is to provide a method for treating  
28 Attention-Deficit Disorder comprising administering orally to a human diagnosed  
29 as having the disorder at a sustained and increasing dose of 100 ng to 500 mg  
30 over 16 hours a central nervous system drug for treating the disorder in a  
31 human patient and at a minimum number of doses per day.

1 Another object of the invention is to administer a central nervous system  
2 acting drug by a method wherein the drug ascends initially and continuously  
3 over the entire dosing interval for treating Attention-Deficit Disorder, ADD, and  
4 Attention-Deficit Hyperactivity Disorder, ADHD.

5 These objects, as well as other objects, features, and advantages of the  
6 invention will become more apparent from the following detailed disclosure of  
7 the invention and the accompanying claims.

8

9 **DRAWING FIGURES PROVIDED BY THE INVENTION**

10

11 In Figure 1, the solid line depicts the plasma concentration for a central  
12 nervous system stimulant administered from an immediate release form, and  
13 the dotted line denotes the plasma concentration for a central nervous system  
14 stimulant released from a sustained nonascending form.

15 In Figure 2, an immediate release dosage form is depicted by the solid  
16 line comprising a peak and a valley depicted against a sustained release  
17 ascending dose shown by the dotted line.

18 In Figures 3, 4, and 5, the release results are depicted for a central  
19 nervous system drug wherein the clear circles denote a placebo, the dark  
20 circles denote an immediate release form, the dark squares denote a  
21 sustained-nonascending release profile, and clear squares denote a sustained  
22 ascending release rate profile.

23 In Figure 6, a sustained-ascending release plasma concentration is  
24 depicted by the solid line and compared with an immediate-release plasma  
25 concentration depicted by the dash line comprising the peaks and valleys.

26 In Figure 7, the solid circles denote a placebo, the clear circles a  
27 sustained-ascending profile, and the solid squares a three-times-a-day program  
28 for the same central nervous system drug.



1           Figure 8 depicts a placebo given three times a day comprising dark  
2   circles, an immediate-release depicted by solid squares, and a sustained-  
3   ascending release essentially free of tolerance by clear circles for the same  
4   drug.

5           Figures 9-11 depict the plasma methylphenidate concentration obtained  
6   by administering the drug three times a day, in an ascending dose, and by a  
7   dosage form that controls the delivery profile.

8           Figures 12-16 depict the plasma methylphenidate concentration  
9   obtained by administering the drug from a dosage form comprising an external  
10   overcoat initial dose of drug followed by an internal ascending dose of drug  
11   over time.

#### 12 13                   DETAILED DISCLOSURE OF SPECIFICATION 14

15           In accordance with the practice of this invention, it has now been found  
16   that a dosage form and a method can be provided that administers a drug in a  
17   novel program that substantially lessens or completely compensates for  
18   tolerance in a patient. Tolerance, as defined in Pharmacology in Medicine,  
19   by Brill, p. 227 (1965) McGraw-Hill, is characterized as a decrease in effect  
20   followed by administering a drug. When tolerance develops following a single  
21   dose or a few doses over a very short time, it is referred to as acute tolerance.  
22   When the drug is administered over a more protracted period of time to show a  
23   demonstrable degree of tolerance, it is referred to as chronic tolerance. The  
24   medical literature, as exemplified in, The Pharmacological Bases of  
25   Therapeutics, by Goodman and Gilman, 8th Ed., p. 72 (1990) Pergamon Press,  
26   reported tolerance may be acquired to the effects of many drugs and this  
27   literature classifies tolerance as acute or chronic based on when it is acquired.  
28   That is, acute tolerance develops during a dosing phase of one dose or on one  
29   day, and chronic tolerance is acquired due to chronic administration typically  
30   weeks, months, and years. Tolerance as presented in medical literature most  
31   frequently denotes chronic tolerance as seen by administering larger doses

1 over a long time, often necessitated by an increase in body dimensions, hepatic  
2 enzyme involved in biotransformation, and the like.

3 The invention comprises dosage forms for providing an ascending dose  
4 of drug. Representative of a dosage form comprises a hydrogel matrix  
5 containing a plurality of tiny pills. The hydrogel matrix comprises a hydrophilic  
6 polymer selected from the group consisting of a polysaccharide, agar, agarose,  
7 natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan,  
8 furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, gum  
9 tragacanth, locust bean gum, pectin, amylopectin, gelatin and a hydrophilic  
10 colloid. The hydrogel matrix comprises a plurality of 4 to 50 tiny pills, each tiny  
11 pill comprising an increasing dose population of from 100 ng ascending in dose  
12 such as 0.5 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, etc. The tiny pills  
13 comprise a release rate controlling wall of 0.0 mm to 10 mm thickness to  
14 provide for the timed ascending release of drug. Representative of wall-forming  
15 materials include a triglyceryl ester selected from the group consisting of  
16 glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl  
17 laureate, glyceryl didecenoate and glyceryl tridecenoate. Other wall forming  
18 materials comprise polyvinyl acetate phthalate, methylcellulose phthalate, and  
19 microporous vinyl olefins. Procedures for manufacturing tiny pills are disclosed  
20 in U.S. Patent Nos. 4,434,153; 4,721,613; 4,853,229; 2,996,431; 3,139,383  
21 and 4,752,470.

22 The dosage form of the invention for delivering an ascending dose of  
23 drug comprises drug releasing beads. The drug releasing beads are  
24 characterized by a dissolution profile wherein 0 to 20% of the beads undergo  
25 dissolution and release the drug in 0 to 2 hours, 20 to 40% undergo dissolution  
26 and release the drug in 2 to 4 hours, 40 to 60% exhibit dissolution and release  
27 in 4 to 6 hours, 60 to 80% in 6 to 8 hours, and 80 to 100% in 8 to 10 hours.  
28 The drug releasing beads comprise a central composition or core comprising a  
29 drug and pharmaceutically acceptable composition forming ingredients  
30 including a lubricant, antioxidant, and buffer. The beads comprise increasing  
31 doses of drug, for example, 1 mg, 2 mg, 5 mg, and 10 mg, increasing to 40 mg.

1 The beads are coated with a release rate controlling polymer that can be  
2 selected utilizing the dissolution profile disclosed above. The manufacture of  
3 beads is disclosed in Inter. J. of Pharm., by Liu, Vol. 112, pp. 105-116 (1994);  
4 Inter. J. of Pharm., by Liu and Yu, Vol. 112, pp. 117-124 (1994); Pharm. Sci.,  
5 by Remington, 14th Ed. pp. 1626-1628 (1970); J. Pharm. Sci., by Fincher,  
6 Vol. 57, pp. 1825-1835 (1968); and U.S. Patent No. 4,083,949.

7 A dosage form provided by the invention comprises a concentration  
8 gradient of drug from 1 mg to 100 mg coated from the former low dose to the  
9 latter high dose on a polymer substrate. The polymer can be erodible or a  
10 nonerodible polymer. The coated substrate is rolled about itself from the latter  
11 high dose at the center of the dosage form, to the former low dose at the  
12 exposed outer end of the substrate. The coated substrate is rolled from the  
13 high dose to the low dose to provide for the release of from low to high dose  
14 as the substrate unrolls or erodes. For example, 1 mg to 25 mg of  
15 methylphenidate is coated onto an erodible polymer such as an polypeptide,  
16 collagen, gelatin, or polyvinyl alcohol, and the substrate rolled concentrically  
17 from the high dose rolled over and inward to adapt a center position, and then  
18 outward towards the low dose to form an outer position. In operation, the  
19 dosage form erodes dispensing an ascending dose of methylphenidate that  
20 is released over time.

21 Another dosage form provided by the invention comprises a multiplicity  
22 of layers, wherein each layer is characterized by an increasing dose of drug.  
23 The phrase "multiplicity of layers" denotes 2 to 6 layers in contacting lamination.  
24 The multiplicity of layers are positioned consecutively, that is, one layer after  
25 another in order, with a first exposed layer, the sixth layer in contact with the  
26 fifth layer and its exposed surface coated with a drug impermeable polymer.  
27 The sixth layer is coated with a drug impermeable polymer to insure release of  
28 drug from the first layer to the sixth layer. The first layer comprises 1 to 5 mg of  
29 drug and each successive layer comprises an additional 1 to 5 mg of drug.  
30 The biodegradable polymers undergo chemical decomposition to form soluble  
31 monomers or soluble polymer units. The biodegradation of polymers usually

1 involves chemically or enzymatically catalyzed hydrolysis. Representative of  
2 biodegradable polymers acceptable for an increase drug loading in each layer  
3 of from 5 to 50 wt% over the first and successive layers wherein the first layer  
4 comprises 100 ng. Representative biodegradable polymers comprise a  
5 member selected from the group consisting of biodegradable poly(amides),  
6 poly(amino acids), poly(esters), poly(lactic acid), poly(glycolic acid),  
7 poly(orthoesters), poly(anhydrides), biodegradable poly(dehydropyrans), and  
8 poly(dioxinones). The polymers are known to the art in Controlled Release of  
9 Drugs, by Rosoff, Ch. 2, pp. 53-95 (1989); and in U.S. Patent Nos. 3,811,444;  
10 3,962,414; 4,066,747; 4,070,347; 4,079,038; and 4,093,709.

11 The invention further employs a dosage form comprising a polymer that  
12 releases a drug by diffusion, flux through pores, or by rupture of a polymer  
13 matrix. The drug delivery polymeric system comprises a concentration  
14 gradient, wherein the gradient is an ascent in concentration from a beginning  
15 or initial concentration to a final, or higher concentration of 100 ng to 250 mg.  
16 The dosage form comprises an exposed surface at the beginning dose and a  
17 distant nonexposed surface at the final dose. The nonexposed surface is  
18 coated with a pharmaceutically acceptable material impermeable to the  
19 passage of drug. The dosage form structure provides for a flux increase  
20 delivery of drug ascending from the beginning to the final delivered dose.

21 The dosage form matrix can be made by procedures known to the  
22 polymer art. In one manufacture, 3 to 5 or more casting compositions are  
23 independently prepared wherein each casting composition comprises an  
24 increasing dose of drug with each composition overlaid from a low to the  
25 high dose. This provides a series of layers that come together to provide a  
26 unit polymer matrix with a concentration gradient. In another manufacture,  
27 the higher dose is cast first followed by laminating with layers of decreasing  
28 dose to provide a polymer matrix with a drug concentration gradient. An  
29 example of providing a dosage form comprises blending a pharmaceutically  
30 acceptable carrier, like polyethylene glycol, with a known dose of drug, like a  
31 central nervous system stimulant, at an elevated temperature, like 37°C, and

1 adding it to a silastic medical grade elastomer with a cross-linking agent, like  
2 stannous octanoate, followed by casting in a mold. The step is repeated for  
3 each successive layer. The system is allowed to set, for 1 hour, to provide the  
4 dosage form. Representative polymers for manufacturing the dosage form  
5 comprise a member selected from the group consisting of olefin and vinyl  
6 polymers, condensation polymers, carbohydrate polymers, and silicon polymers  
7 as represented by poly(ethylene), poly(propylene), poly(vinyl acetate),  
8 poly(methyl acrylate), poly(isobutyl methacrylate), poly(alginate), poly(amide),  
9 and poly(silicone). The polymers and manufacturing procedures are known in  
10 Polymers, by Coleman et al., Vol. 31, pp. 1187-1230 (1990); Drug Carrier  
11 Systems, by Roerdink et al., Vol. 9, pp. 57-109 (1989); Adv. Drug Delivery Rev.,  
12 by Leong et al., Vol. 1, pp. 199-233 (1987); Handbook of Common Polymers,  
13 Compiled by Roff et al., (1971) published by CRC Press; and U.S. Patent  
14 No. 3,992,518.

15 Further in accord with the practice of the present invention, the method  
16 of this invention uses the disclosed dosage forms for administering a drug to a  
17 patient that may acquire acute or chronic tolerance for decreasing and/or  
18 avoiding said tolerance, and presently the method is indicated for treating  
19 patients that may acquire acute tolerance. Further, in accordance with the  
20 practice of this invention, in one embodiment, it has also been found a method  
21 can be provided that administers a drug for treating Attention-Deficit Disorder,  
22 to a human orally as a function of time to achieve the desired drug  
23 concentration over time. The concentration of drug relates to the dose of drug  
24 in mg per hour delivered per unit time in hours for absorption into the systemic  
25 circulation. The method of the invention uniquely provides a method for  
26 maintaining a desired drug effect by adjusting continually the drug delivery  
27 rate when the therapeutic effect declines during acquired acute tolerance.

28 It is standard medical practice, that a drug should provide a therapeutic  
29 effect throughout the dosing interval. However, when tolerance develops or is  
30 acquired to a drug, the prior art approach to ensure a therapeutic response is to  
31 increase the dose administered in an immediate dose dumping manner, and for

1 this type of dosing, where associated side effects are likely to occur, tolerance  
2 may develop unequally to all the effects, and the therapeutic index may  
3 decrease. Another approach used by the prior art to lessen the occurrence of  
4 tolerance is to administer drug doses less frequently so that acquired tolerance  
5 is avoided, but with this approach there is an absence of therapy for a given  
6 time.

7 In medicine, it is generally accepted that central nervous system acting  
8 drugs are useful for the management of Attention-Deficit Disorders. The drugs  
9 useful for this therapy are the mild central nervous system stimulants, and they  
10 include catecholamines and drugs that can mimic their action. The drugs  
11 useful for this therapy comprise a member selected from the group consisting  
12 of amphetamine, dextro-amphetamine, methamphetamine, methylphenidate,  
13 racemic methylphenidate, threo-methylphenidate, phenylisopropylamine,  
14 risperidone, and pemoline. The drugs include also their pharmaceutically  
15 acceptable salts such as a member selected from the group consisting of  
16 hydrochloride, sulfate, phosphate, acetate, hydrobromide, pamoate, and  
17 maleate. A patient receiving these drugs typically acquires tolerance to the  
18 effects of the drugs. For example, a patient on methylphenidate and receiving  
19 a 5 mg dose twice a day acquires tolerance, and a larger dose must be  
20 administered due to the single large dose needed to overcome the tolerance  
21 development which would give rise to unwanted side effects. In some patients,  
22 the therapeutic response to methylphenidate declines in 4 to 5 hours despite  
23 the maintenance of methylphenidate in a nonascending constant concentration.  
24 That is, tolerance is acquired to the behavioral and psychological effects of  
25 methylphenidate and generally to psychostimulants. This invention has found  
26 also that a sustained release product that dispenses a noncompensating but  
27 constant concentration of a drug will not be clinically effective, as a sustained-  
28 release dosage form designed to produce a constant plasma of, for example,  
29 methylphenidate concentration, lacks efficacy particularly against acquired  
30 tolerance.

1        This invention among its objects provides a dosage form and method for  
2        treating Attention-Deficit Disorders, which include Attention-Deficit/Hyperactivity  
3        Disorder, combined type, predominantly inattentive type, predominantly  
4        hyperactive impulsive type and which are known also as minimal brain  
5        dysfunction, hyperkinetic child syndrome, behavioral syndrome, minimal  
6        cerebral dysfunction and minor cerebral dysfunction, as disclosed in the  
7        Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, pp. 49-56  
8        (1987) published by the American Psychiatric Association, Washington, D.C.,  
9        by making available both a dosage form and a method of treatment that  
10       substantially negates the unwanted results of the prior art by providing  
11       continuous compensation of drug to essentially eliminate acute tolerance,  
12       thereby producing a stabilization of the therapeutic effect.

13       The pharmacological effect of a drug is related to its receptor site  
14       concentration. Thus, when the effect of a drug is considered as a function (f)  
15       of delivery time (t), the kinetics of stabilization for some drugs can be rapid,  
16       and for other drugs the effect does not stabilize as a diminution in response  
17       expressed as tolerance develops to the drug. This latter condition applies to  
18       central nervous system acting drugs such as methylphenidate. This invention  
19       compensates for acquired-acute tolerance by providing an optimal drug delivery  
20       profile for its management. For some drugs the onset of tolerance is quick,  
21       for instance, tolerance develops for methylphenidate within hours after its  
22       administration. A management program for this is provided by this invention by  
23       making available a drug delivery pattern that initially delivers a dose of drug to  
24       achieve instant therapy and accompanied by a sustained-ascending release  
25       dose over time to maintain the effect.

26       The drug methylphenidate is commercially available in a sustained  
27       release dosage form Ritalin®-SR, and the methylphenidate dispensed by this  
28       commercial form can lead to acute tolerance. When acute tolerance is  
29       acquired a drug-free washout period of several hours is needed before a repeat  
30       administration is likely with the dosage form. The present invention however,

1 compensates for the loss of a therapeutic effect of a drug, such as  
2 methylphenidate, by providing a method of delivery rate in mg per hour  
3 that continually compensates for the development of acute tolerance,  
4 by considering the clinical effect (E) of a drug at time (t) as a function of  
5 the drug concentration (C) according to Equation 1:

6

$$7 \quad \text{Effect} = f(t, C) \quad \text{Eq. 1}$$

8

9 In addition, the rate of drug delivered (A), in mg per hour is directly  
10 proportional to the concentration times the clearance of the drug. As the  
11 effect varies with time and the functionality is expressed, then according  
12 to this invention (A) can be governed to ensure the therapeutic effect is  
13 maintained at a clinical value. If the effect from a drug is found clinically to  
14 decrease with time, this decline could be linear as expressed by Equation 2:

15

$$16 \quad \text{Effect}_{(t)} = \text{Effect}_{(ini)} - k_{\text{Effect}} * t \quad \text{Eq. 2}$$

17

18 wherein,  $\text{Effect}_{(ini)}$  is the clinical effect observed initially at the start of drug  
19 administration and  $\text{Effect}_{(t)}$  is the effect observed at time (t) hours,  $k_{\text{effect}}$  is a  
20 proportionality constant ascertained by measuring the clinical effect (E1)  
21 at time (t1) hours and (E2) at time (t2) hours while maintaining a constant  
22 plasma concentration followed by dividing (E1) minus (E2) by (t1) minus (t2).  
23 In order to maintain a constant effect, (A) must be adjusted with the same  
24 functionality according to Equation 3:

25

$$26 \quad A_{(t)} = A_{(ini)} + k_{\text{Effect}} * t \quad \text{Eq. 3}$$

27

28 wherein  $A_{(ini)}$  is the initial drug input in mg per hour at the start of the therapy  
29 and  $A_{(t)}$  is the drug input at time (t) hours, and  $k_{\text{Effect}}$  is the proportionality  
30 constant presented above. If the therapeutic effect is found to decline  
31 exponentially with time, this relationship is expressed by Equation 4:



$$\text{Effect}_{(t)} = \text{Effect}_{(in)} * \exp^{(-k_{\text{Effect}} * t)} \quad \text{Eq. 4}$$

wherein  $\text{Effect}_{(in)}$  and  $\text{Effect}_{(t)}$  are as defined before,  $k_{\text{Effect}}$  is a rate constant ( $\text{h}^{-1}$ ), a unit of reciprocal hours, ascertained by measuring the clinical effect (E1) at time ( $t_1$ ) hours and (E2) at time ( $t_2$ ) hours while maintaining a constant plasma concentration followed by dividing natural log of (E1) minus natural log of (E2) by ( $t_1$ ) minus ( $t_2$ ). To maintain a constant effect, (A) must be adjusted according to Equation 5:

$$A_{(t)} = A_{(in)} * \exp^{(k_{\text{Effect}} * t)} \quad \text{Eq. 5}$$

wherein  $A_{(in)}$  and  $A_{(t)}$  is as defined before.  $k_{\text{Effect}}$  is the rate constant ( $\text{h}^{-1}$ ) presented above. The equations are presented in Pharmac. Ther., Vol. 16, pp. 143-166 (1982) by Holford N.H.G. and Sheiner, L.E.

The effects defined herein refer to the pharmacological effects exhibited by the drug as ascertained by clinical subjective observation such as SKAMP and CLAM, or as ascertained by objective activity monitoring such as mathematic tests and school accomplishments. The CLAM Test is a behavior rating that indicates social conformity or rebellion as developed by Connors, Loney, and Milch and SKAMP is a rating that also measures behavior as developed by Swanson and reported in Psychopharmacological Bulletin, Vol. 21, pp. 887-890 (1985).

The effect measurements in this study were: (1) observer ratings on SKAMP scale (during classroom time) and (2) performance on the computerized mathematics test. Each child was tested on the mathematics test before the study began, and based on this pre-test during the study, a mathematics test appropriate for each child's ability was given. The morning and evening parent CLAM assessments were used to identify unusual behaviors. The evening parent CLAM was used to determine the presence of treatment effects in the evening hours, particularly treatment effects on the

1 time the child fell asleep, and whether the child's sleep was interrupted. All of  
2 the children also wore an activity monitor (Actigraph) which records the  
3 movements of the child throughout the day. The activity (number of  
4 movements per minute) is recorded electronically and modeled as a function  
5 of the drug effect.

6  
7 **DETAILED DISCLOSURE OF EXAMPLES**  
8 **PROVIDED BY THE INVENTION**  
9

10 The following examples are merely illustrative of the present invention  
11 and they should not be considered as limiting the scope of this invention in  
12 any way, as these examples and other equivalents thereof will become  
13 apparent to those versed in the art in the light of the present disclosure  
14 and the accompanying claims.

15  
16 **EXAMPLE 1**  
17

18 A commercially available immediate release tablet consisting of 5 mg  
19 of methylphenidate was administered twice a day to 36 school children, and  
20 the predicted plasma concentration in ng/ml graphed against time as seen in  
21 the solid black line in Figure 1. The tablet exhibits a peak and valley plasma  
22 concentration for the methylphenidate. A sustained-release nonascending  
23 program that administered 20 mg of methylphenidate consisting of 8.3 mg  
24 at zero hour followed by 0.9 mg at 1.5 hours, 0.9 mg at 2 hours, 0.9 mg  
25 2.5 hours, 0.9 mg at 3 hours, 0.9 mg at 3.5 hours, 0.9 mg at 4 hours, 0.9 mg  
26 at 4.5 hours, 0.9 mg at 5 hours, 0.9 mg at 5.5 hours, 0.9 mg at 6 hours,  
27 0.9 mg at 6.5 hours, 0.9 mg at 7 hours, and 0.9 mg at 7.5 hours produced  
28 the sustained-release dotted line parallel to the x-axis as seen in Figure 1.  
29 The immediate release tablet and the sustained-release dosage form were  
30 compared to a sustained-release dosage form that administered  
31 methylphenidate in an ascending profile. The sustained-release ascending

1 profile corresponds to administering 4.2 mg at zero hour, 1.1 mg at 1.5 hours,  
2 1.1 mg at 2 hours, 1.2 mg at 2.5 hours, 1.2 mg at 3.0 hours, 1.3 mg at  
3 3.5 hours, 1.3 mg at 4 hours, 1.5 mg at 4.5 hours, 1.5 mg at 5 hours, 1.8 mg  
4 at 5.5 hours, 1.8 mg at 6 hours, and 2.0 mg at 6.5 hours, to produce the  
5 sustained-ascending release dotted line profile seen in Figure 2.

6 The results of the clinical studies demonstrated patients administered a  
7 dosage form free of methylphenidate, a placebo, exhibited high, elevated  
8 swings in behavior, such as activity, inappropriate behavior, low attention,  
9 lower mathematical scores and a disinterest in school. The patients  
10 administered a sustained-nonascending dose of methylphenidate exhibited a  
11 decrease in activity, higher mathematical scores and a lessening of  
12 inappropriate behavior. However, these effects were accompanied by the  
13 development of acute tolerance in the patient. The patient administered  
14 methylphenidate, according to this invention, in a controlled-sustained  
15 ascending profile exhibited the desired therapeutic effect without tolerance.  
16 The accompanying figures present the results of the above-described study.  
17 In Figures 3, 4, and 5, the line with a clear circle denotes a placebo, the dark  
18 circle an immediate release dosage form administered twice a day, the dark  
19 squares a sustained release nonascending dosage profile, and the clear  
20 squares the sustained ascending release profile provided by this invention.  
21 The SKAMP Score and CLAM Score were defined earlier in the specification,  
22 and the times are as indicated on the figures. Figure 3 denotes the observed  
23 behavior, Figure 4 denotes the inattention overactivity, and Figure 5 denotes  
24 the combined attention results of the study.

25

26

## EXAMPLE 2

27

28 The results of a clinical study that comprises administering  
29 methylphenidate according to two distinct delivery programs are reported in  
30 this example. In the study, a sustained-ascending profile corresponds to  
31 administering methylphenidate as follows: 8 mg at zero hours, 1.4 mg at

1 1.5 hours, 1.4 mg at 2.0 hours, 1.7 mg at 2.5 hours, 1.7 mg at 3.0 hours,  
2 2.0 mg at 3.5 hours, 2.0 mg at 4.0 hours, 2.2 mg at 4.5 hours, 2.2 mg at  
3 5.0 hours, 2.2 mg at 5.5 hours, 2.2 mg at 6.0 hours, 2.4 mg at 6.5 hours,  
4 2.4 mg at 7.0 hours, 2.6 mg at 7.5 hours, and 1.9 mg at 8.0 hours. The  
5 methylphenidate was administered in overcoated capsules comprising a  
6 total of 36 mg of methylphenidate with 22% in the exterior overcoat. The  
7 ascending dose was administered with the first dose at 0730 followed by  
8 ascending doses every 30 minutes until 1530 to produce the intended  
9 ascending plasma concentration. The study included the delivery of  
10 methylphenidate in immediate dosage form three times a day with 10 mg of  
11 methylphenidate delivered at 0730, 1130, and 1530 hours. The study was  
12 done with 32 children with attention deficient hyperactivity disorder.  
13 Accompanying Figure 6 depicts the plasma concentration for methylphenidate  
14 wherein the dot-dash line is produced by the sustained-ascending  
15 administration program, and the dash line is produced by the immediate  
16 dosage form. In accompanying Figure 7, the solid circles denote placebos,  
17 the clear circles denote the sustained-ascending program, the solid squares  
18 denote the three times a day program, and the parameter observed was  
19 behavior with an absence of acquired tolerance for the sustained ascending  
20 program. Accompanying Figure 8 depicts the combined attention parameter  
21 wherein the solid circle is a placebo with acquired tolerance, the solid square  
22 is the three daily immediate release delivery with acquired tolerance, and the  
23 clear circle is the sustained-ascending release essentially free of developed  
24 tolerance.

25

26

### EXAMPLE 3

27

28 A method for administering the central nervous system stimulant  
29 methylphenidate in a sustained and ascending dose for the management of  
30 attention deficient disorder accompanied by a lessening of acquired tolerance  
31 is provided by administering a dosage form shaped as an orally administered

1 tablet. The dosage form comprises a film of polyanhydride polymer of  
2 sebacic and azelaic acids coated with a composition comprising 20 mg of  
3 methylphenidate blended with pharmaceutically acceptable gelatin. The  
4 pharmaceutically acceptable film is coated with the methylphenidate  
5 composition in increased thickness spirally wound about itself. Following oral  
6 administration into the gastrointestinal tract the composition comprising the  
7 methylphenidate is dispensed at constantly increasing rate as the film erodes  
8 over time. The polymer of the dosage form is described in U.S. Patent  
9 Nos. 2,668,162 and 2,676,945, and the dosage form is described in  
10 U.S. Patent No. 3,625,214.

11

12

#### EXAMPLE 4

13

14 A method for treating Attention-Deficit Disorder with hyperactivity  
15 supported by psychological and educational guidance by administering  
16 pemoline for a stabilizing effect in children accompanied by an apparent  
17 absence of acquired tolerance is provided by administering a bioerodible  
18 dosage form according to the invention, comprising the central nervous  
19 stimulant pemoline. The dosage form comprises 5 contacting layers of  
20 bioerodible poly(lactide-co-glycolide) with each layer containing an increased  
21 amount of 4, 6, 8, 10 and 12 mg of pemoline. The layers are compressed into  
22 a laminated tablet-shaped arrangement with a single opened surface to  
23 expose the layer containing 2 mg of pemoline with the remainder of the tablet  
24 surrounded with nonbioerodible copolymeric ethylene-vinyl acetate. So the  
25 layers bioerode in constant succession, a corresponding constantly  
26 increasing dose of pemoline is dispensed over time. The bioerodible  
27 polymers are known in U.S. Patent No. 3,773,919; EPO 0-052-510; and  
28 Canadian Patent No. 1,169,090.

**EXAMPLE 5**

A method for administering a drug in a sustained-increasing release rate is provided by administering a dosage form manufactured as a pharmaceutically acceptable gelatin two-piece joined capsule comprising a multiplicity of spherical beads. The capsule comprises a series of beads consisting of a progression of 1, 1.25, 1.5, 1.75, 2 and 2.25 mg of drug in each different bead coated correspondingly with a progression of 0.5, 1, 1.5, 2.5, 3, and 3.25 mm of polymeric poly(2,2-dioxo-trans-1, 4-cyclohexane dimethylene tetrahydrofuran). As the beads erode in the environment of the gastrointestinal tract they dispense drug in a sustained-ascending release rate over time. The drugs that can be dispensed by this method comprise a member selected from the group consisting of amphetamine, dextroamphetamine, methamphetamine, methylphenidate, phenylisopropylamine and pemoline. Procedures for coating are disclosed in J. Am. Phar. Assoc., Sci. Ed., Vol. 48, pp. 451-454 (1959); and U.S. Patent No. 2,799,241.

**EXAMPLE 6**

A delivery system is provided by the invention which releases the drug resulting in an ascending plasma methylphenidate concentration time profile that substantially overcomes tolerance and maintains the desired pharmacological effect of the stimulant methylphenidate for the desired duration. For example, to achieve an effect-time profile similar to the three doses of immediate release given every 4 hours for 12 hours every day, TID (three times a day), a delivery system which results in the plasma methylphenidate concentrations between the ranges as listed below will overcome tolerance and maintain pharmacological effects. To make a delivery system which is equal to two doses of immediate release given every 4 hours the release rate can be truncated, and similarly, for the longer

1 duration the concentration can be increased. The delivery profile exemplifies  
2 the drug and pharmacological effect. However, the concept of increasing  
3 concentration still remains the same.

4 Table 1 provides this range as a fraction of the simulated TID  
5 concentrations. The attached figures show the ascending profile variations  
6 superimposed on the TID and the reference ascending (ASCEND) treatment  
7 profiles.

8

Time (h)	TID Concentration (ng/MI)	Ascending Profile Range (Fraction of TID Concentration)	
		Low	High
1.5	4.8 (peak)	0.75	0.90
3.0	3.8	1.07	1.37
4.0	2.8(trough)	1.32	2.29
5.5	6.5(peak)	0.80	1.20
7.0	4.8	1.42	1.81
8.0	3.6(trough)	2.17	2.50
9.5	7.0(peak)	1.10	1.23
11.0	5.2	1.00	1.38
12.0	3.9	0.97	1.54
15.0	1.7	1.00	1.94

9

10 The accompanying drawing figures depict the therapeutic benefits  
11 obtained by the invention. Figure 9 illustrates a simulated plasma  
12 methylphenidate concentration profile for three-times-a-day 30 mg dose  
13 (solid line), an ascend treatment of 36 mg (dash line), and an osmotic  
14 controlled 36 mg dose (dot-dash line). Figure 10 depicts the plasma  
15 methylphenidate concentration as in Figure 9, except in Figure 10 the osmotic  
16 controlled dose is 38 mg. Figure 11 depicts the plasma methylphenidate  
17 concentration as in Figure 9, except in Figure 11, the osmotic controlled dose

1 is 40 mg. Figure 12 illustrates 30 mg delivered three times a day by the solid  
2 line, an ascend dose from a dosage form comprising 36 mg of drug once a  
3 day by the dash line, and a dosage form comprising an immediate 8 mg dose  
4 and a sustained 26 mg ascending dose illustrated by the dot-dash line.  
5 Figure 13 depicts a plasma methylphenidate concentration like Figure 12,  
6 except the dosage form represented by the dot-dash line comprises an  
7 instant-release dose of 9 mg of methylphenidate and an ascending dose of  
8 24 mg of methylphenidate. Figure 14 is similar to the previous Figures except  
9 the dot-dash line depicts an instant release dose of 8 mg and an ascending  
10 dose of 25 mg of methylphenidate. Figure 15 is similar to the above Figures,  
11 except the dot dash line illustrates an immediate dose of methylphenidate of  
12 8 mg followed by a sustained ascending dose of 25 mg of methylphenidate.  
13 Figure 16 is similar to the above Figures with the clinical conditions as set  
14 forth, except in this study the dot-dash lines illustrate an immediate dose of  
15 8 mg of methylphenidate, followed by a controlled-ascending dose of 24 mg  
16 of methylphenidate.

17 The method of the invention provides further for administering a drug  
18 according to the above examples, wherein the drug is administered by the  
19 dosage form of this invention in a controlled-rate and in a sustained release  
20 pattern throughout a school day of up to 8 hours, or up to 12 hours.

21 While there has been described and pointed out features and  
22 advantages of the invention, as applied to present embodiments, those skilled  
23 in the medical art will appreciate that various modifications, changes,  
24 additions, and omissions in the method described in the specification can  
25 be made without departing from the spirit of the invention.



1    We Claim:

2

3            1.     A pharmaceutical composition in a dosage form, comprising a  
4     dose of drug in a concentration gradient from a lower to a higher dose that is  
5     released in a lower to a higher dose by the dosage form.

6

7            2.     The dosage form for delivering a drug according to claim 1,  
8     wherein the dosage form comprises: a composition comprising a polymer, a  
9     dose of drug in the composition present in a concentration gradient from a low  
10    to a higher dose, and wherein the dosage form when in operation releases a  
11    low followed by a higher dose of drug.

12

13           3.     The dosage form for delivering a drug according to claim 1,  
14    wherein the dosage form comprises: a multiplicity of layers of a composition  
15    comprising a polymer, a dose of drug in an increasing dose in the multiplicity  
16    of layers, and wherein when the dosage form is in operation, the dosage form  
17    delivers an increasing dose of drug over time.

18

19           4.     The dosage form for delivering a drug according to claim 1,  
20    wherein the dosage form comprises: a plurality of layers comprising a  
21    composition comprising a different polymer, a dose of drug in an increasing  
22    dose in the plurality of layers, and wherein when the dosage form is in  
23    operation, the dosage form delivers an increasing dose of drug over time.

24

25           5.     The dosage form for delivering a drug according to claim 1,  
26    wherein the dosage form comprises: a composition comprising a bioerodible  
27    polymer, a dose of drug in the composition present in an initial dose and a  
28    final dose, whereby the dosage form delivers an initial dose and a final dose  
29    over time.

1           6.     The dosage form for delivering an ascending dose of drug  
2     according to claim 1, wherein the dosage form comprises: a multiplicity of  
3     layers comprising a bioerodible polymer, a drug in an ascending dose in the  
4     layers, whereby the dosage form delivers an ascending dose of drug over  
5     time.

6  
7           7.     The dosage form for delivering an ascending dose of drug  
8     according to claim 1, wherein the dosage form comprises a plurality of layers  
9     comprising a different bioerodible polymer, a drug in an ascending dose in the  
10    different layers, whereby the dosage form delivers an ascending dose of drug  
11    over time.

12  
13          8.     The dosage form for delivering an ascending dose of drug  
14    according to claim 1, wherein the dosage form comprises tiny pills comprising  
15    a drug, which tiny pills release an initial dose of drug and successive  
16    ascending doses of drug over time.

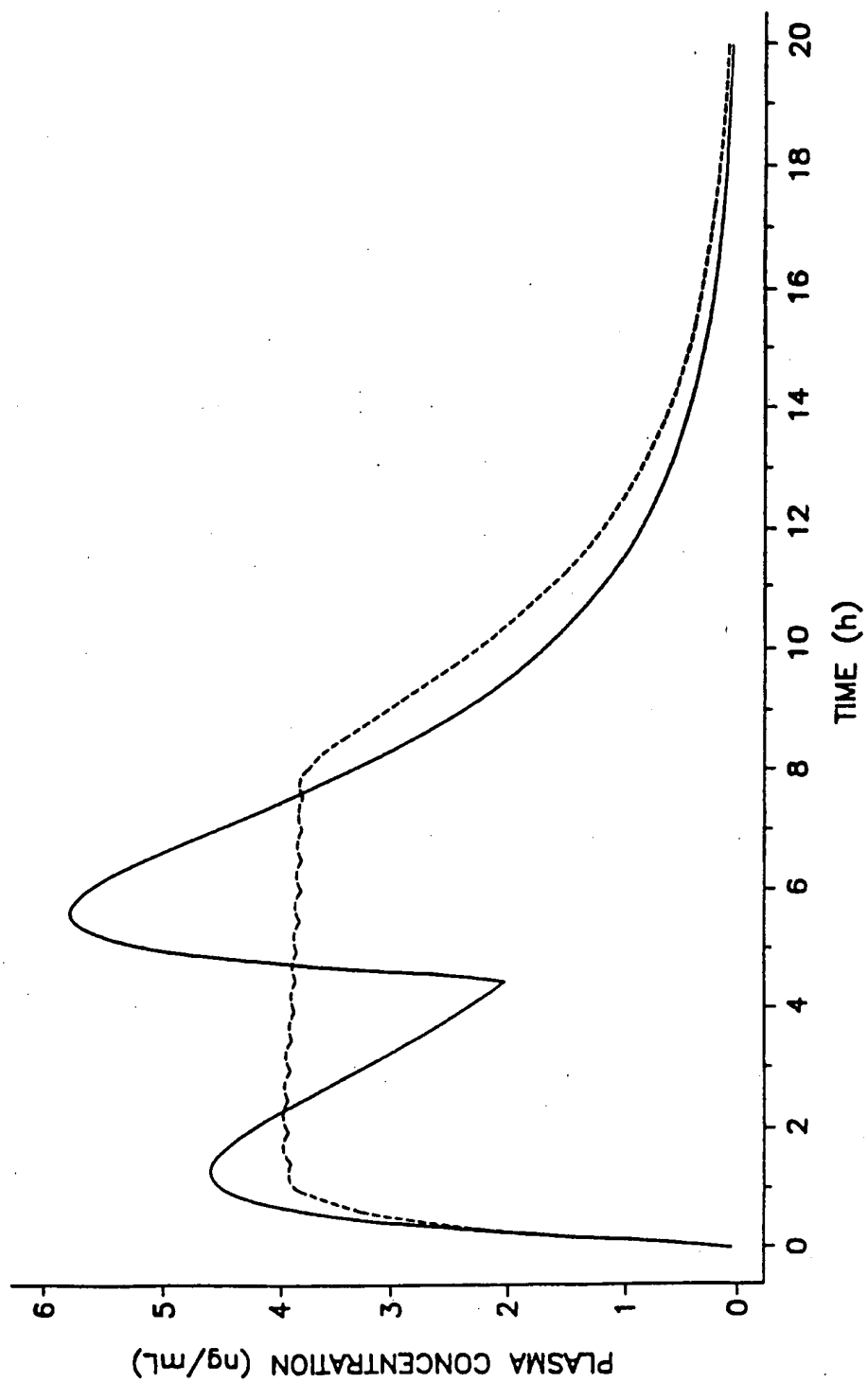
17  
18          9.     The pharmaceutical composition as a dosage form according to  
19    claim 1, wherein the pharmaceutical composition comprises a dose of drug in  
20    admixture with a pharmaceutically acceptable carrier that is released in a  
21    sustained release and increasing dose.

22  
23          10.    The pharmaceutical composition according to claim 1, wherein  
24    the pharmaceutical composition comprises 1 mg to 500 mg of drug.

25  
26          11.    The pharmaceutical composition according to claim 1, wherein  
27    the drug is released in a sustained and increasing dose of 100 ng to 375 mg  
28    over 16 hours.

29  
30          12.    The use of the pharmaceutical composition of claim 1, for the  
31    treatment of psychological disorders.

1 / 16



TIME (h)

FIG. 1

2 / 16

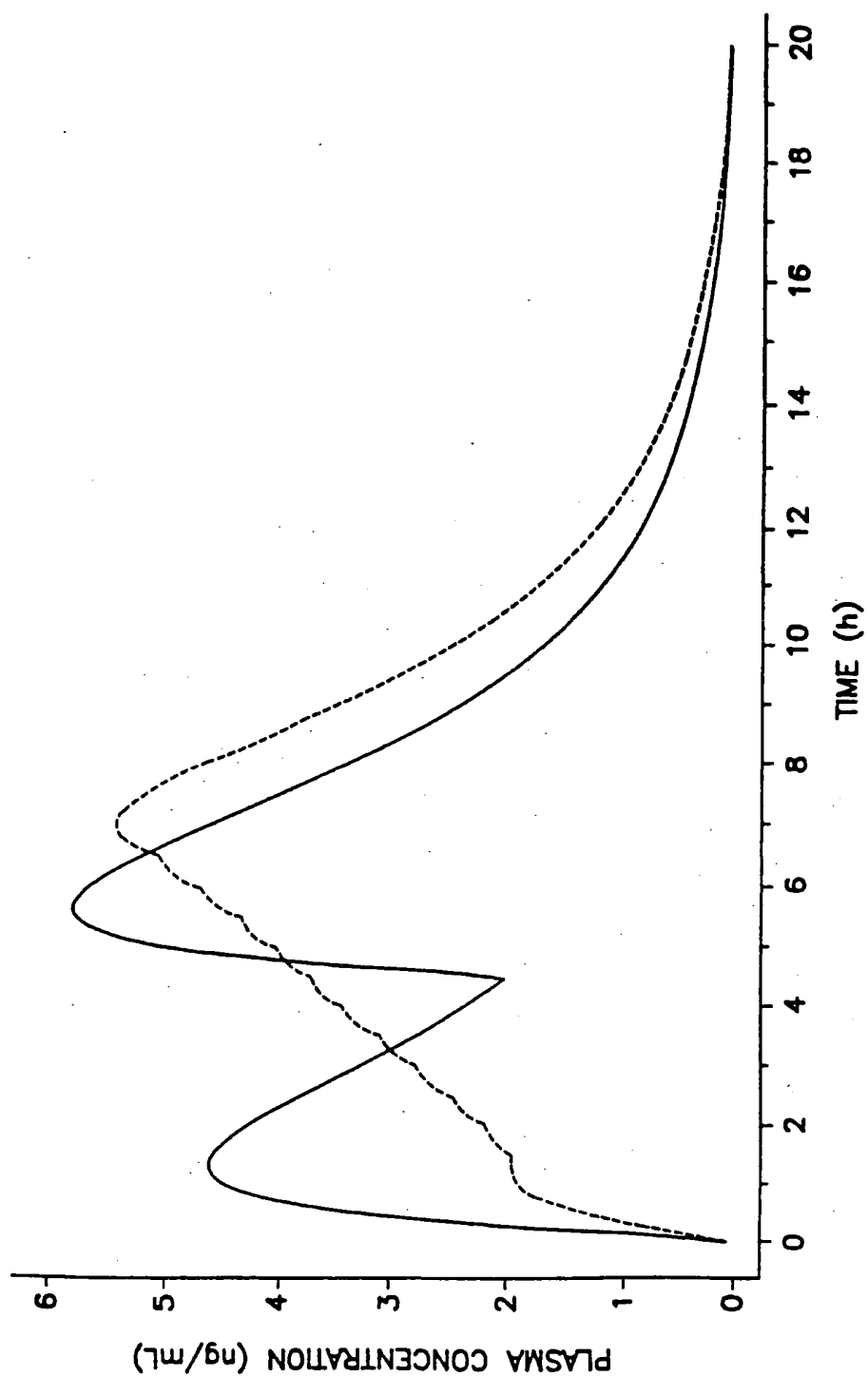


FIG. 2

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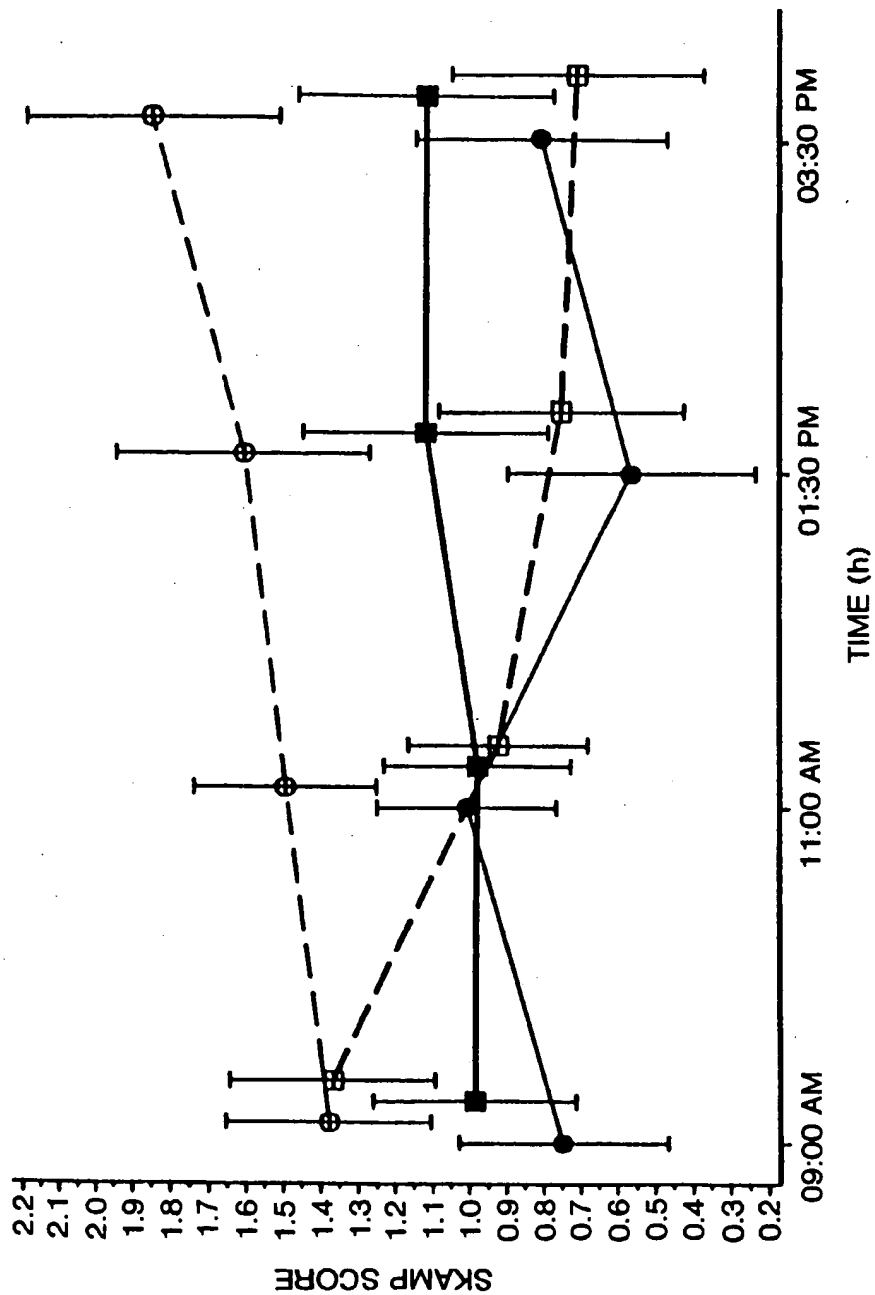


FIG. 3

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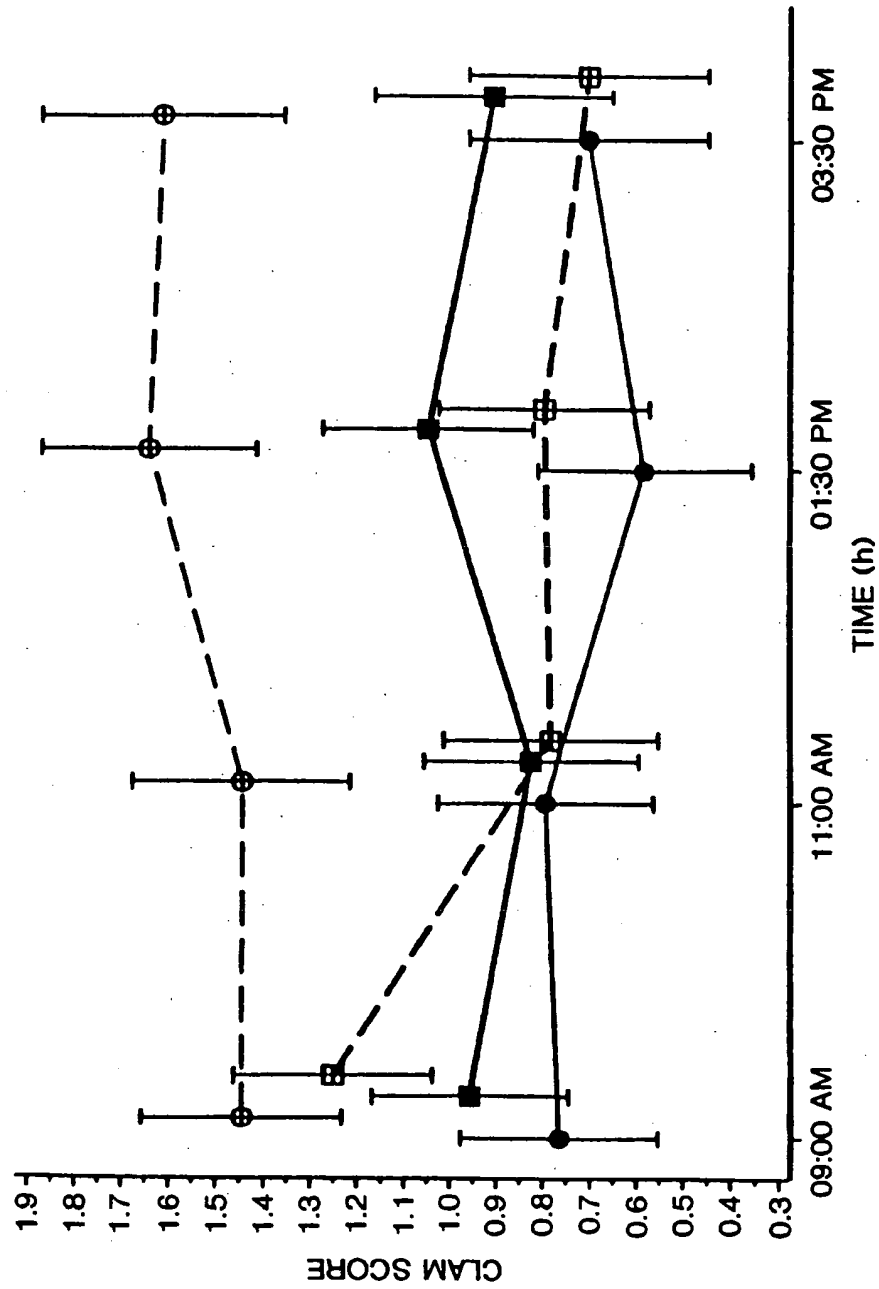


FIG. 4

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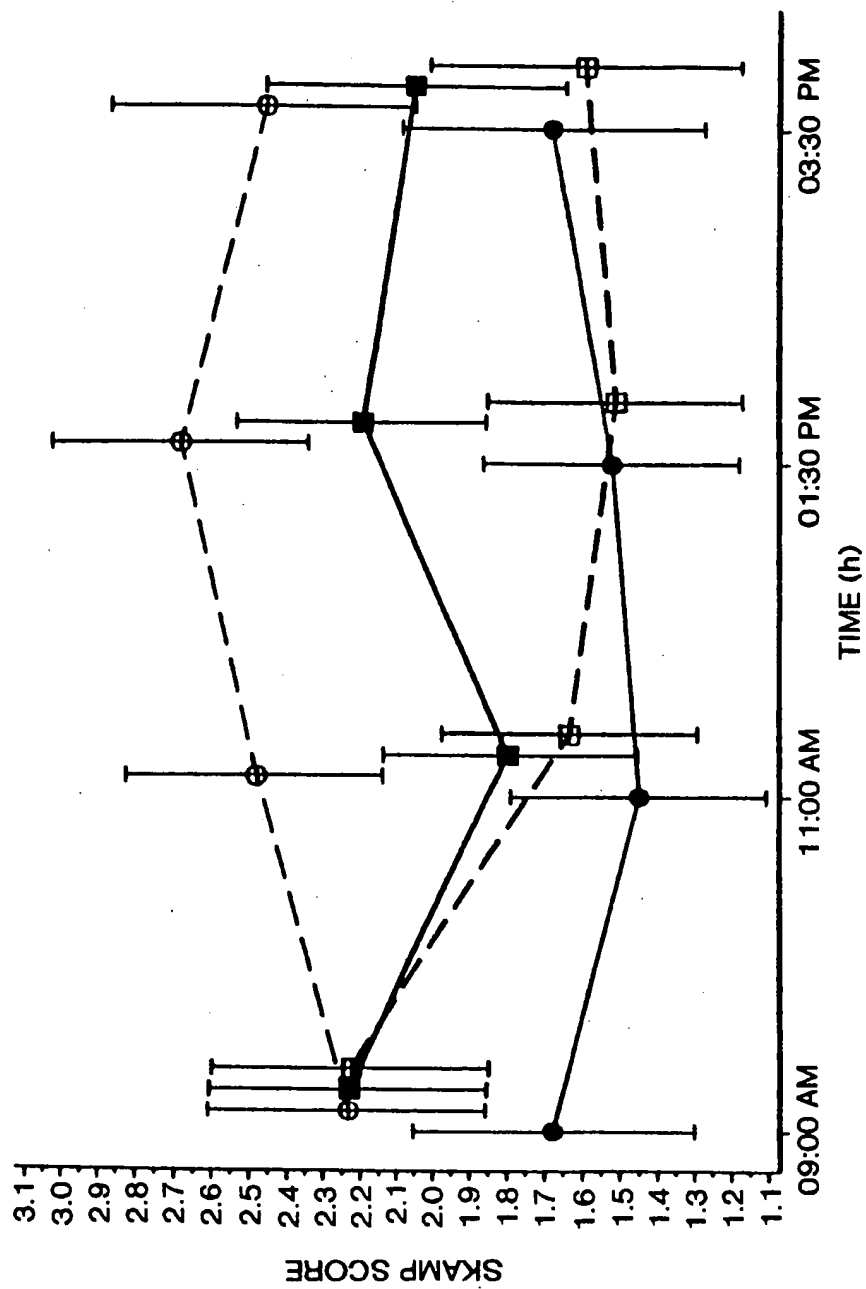


FIG. 5

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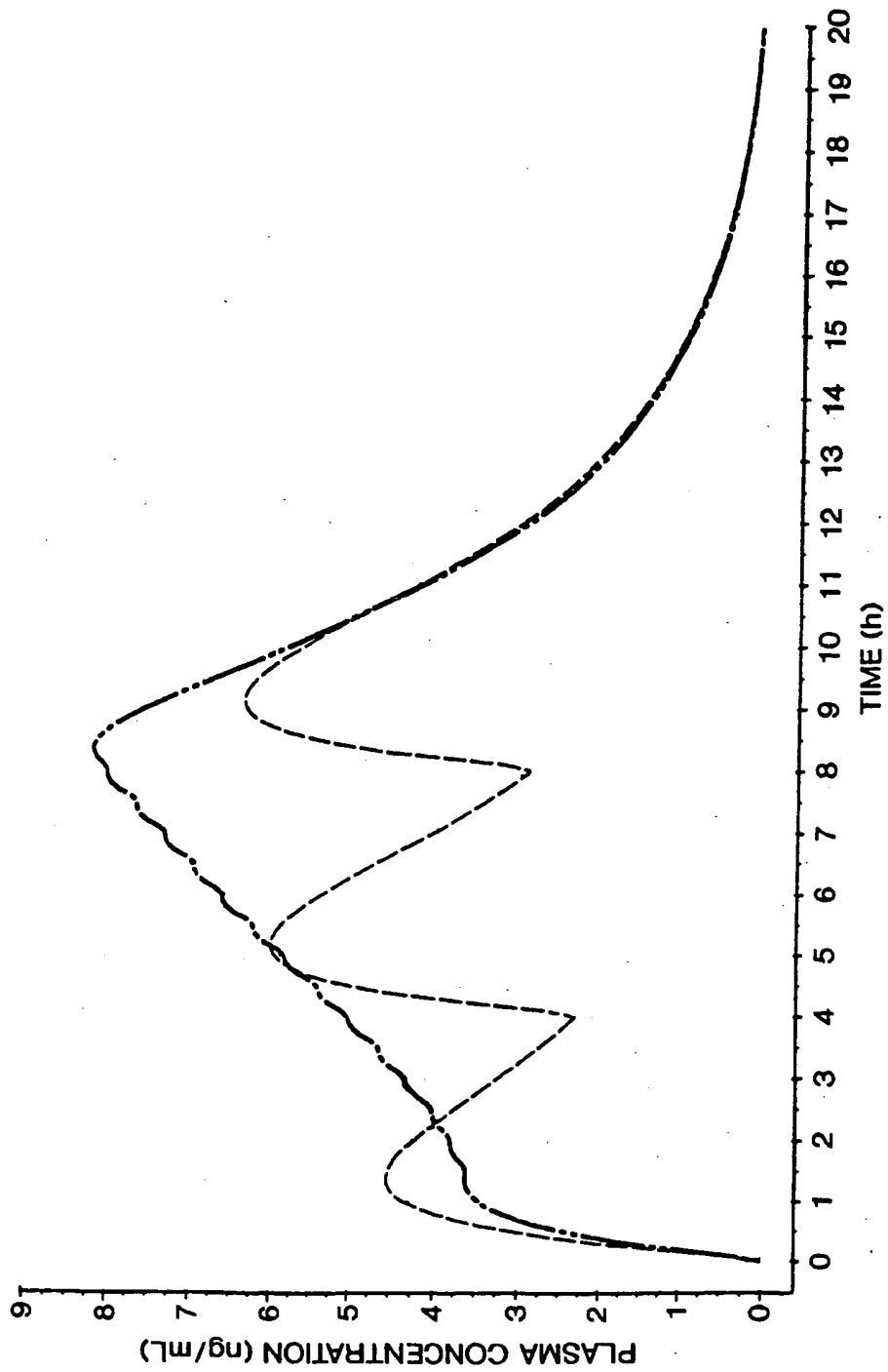


FIG. 6



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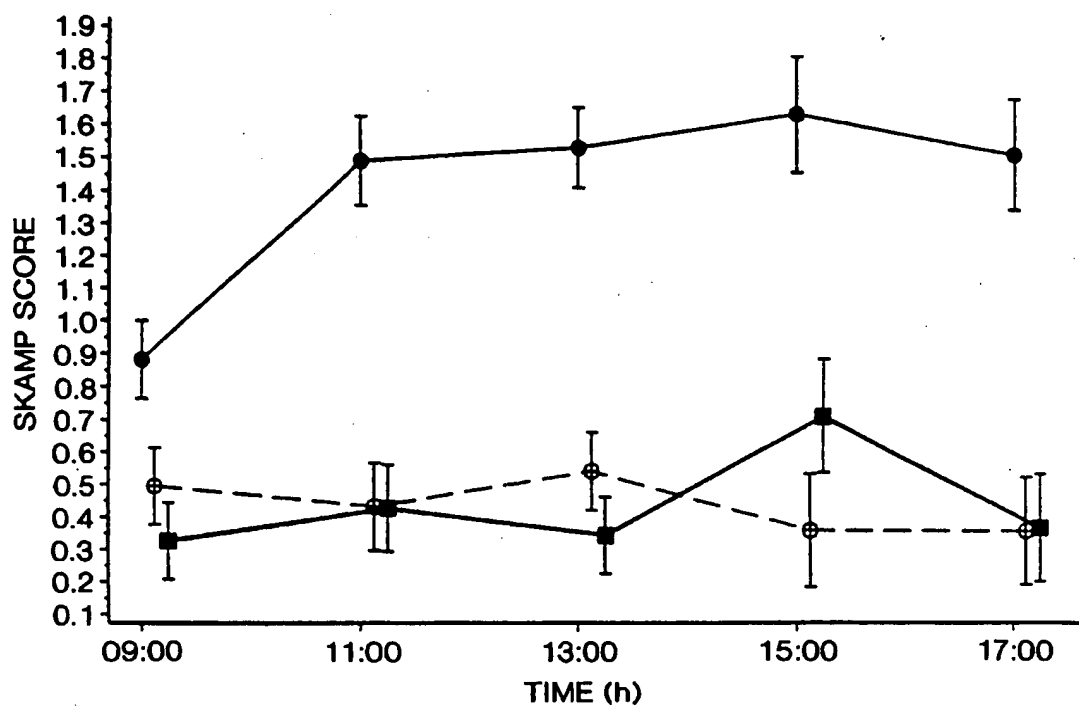


FIG. 7

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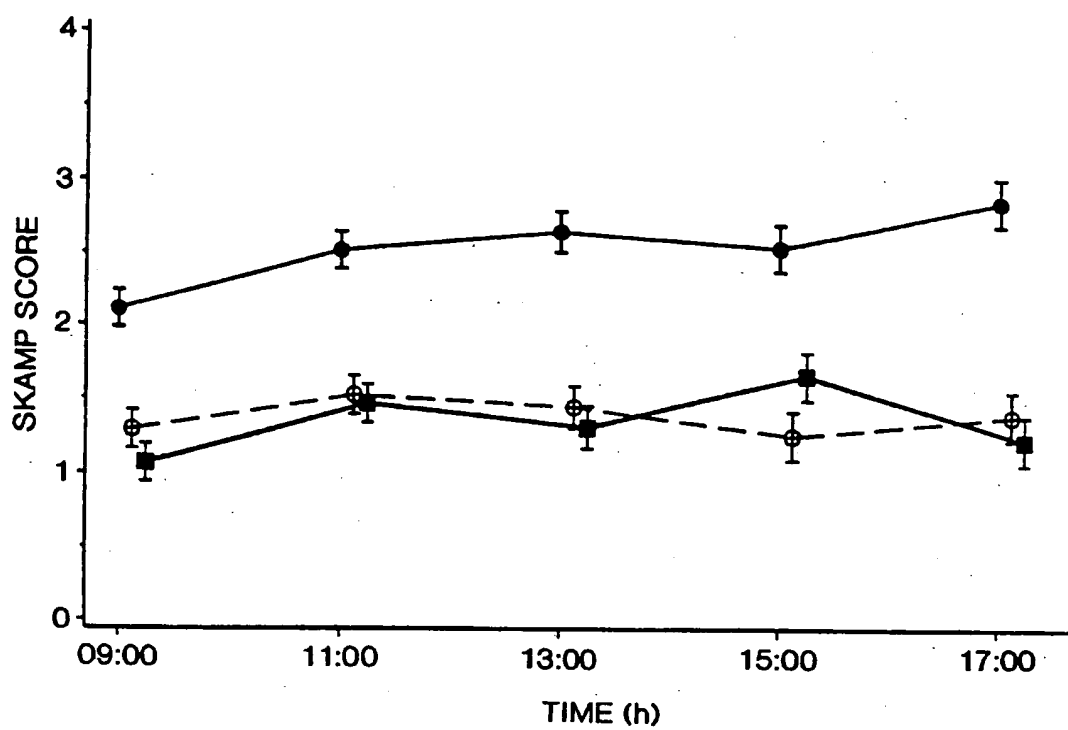


FIG. 8

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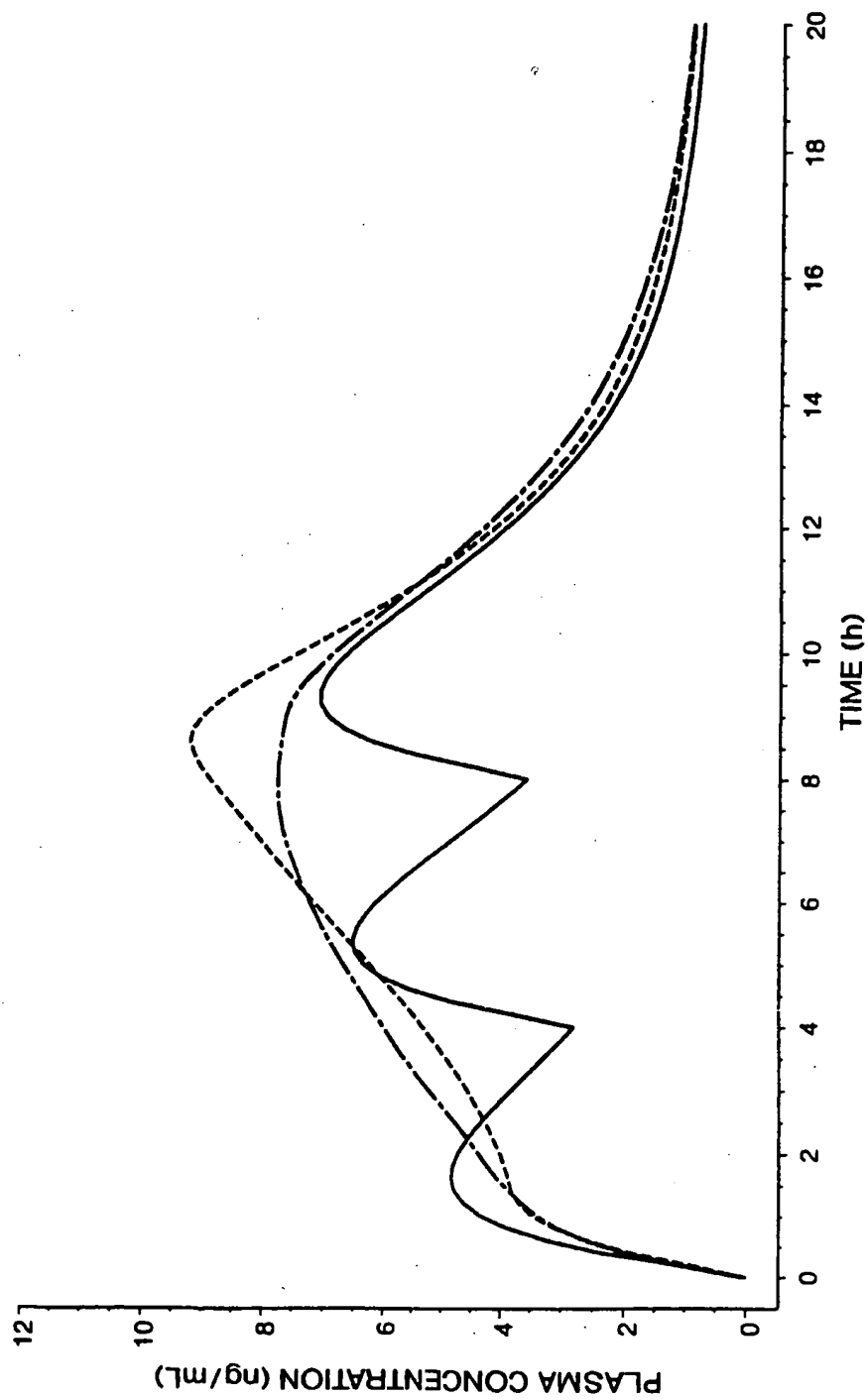


FIG. 9

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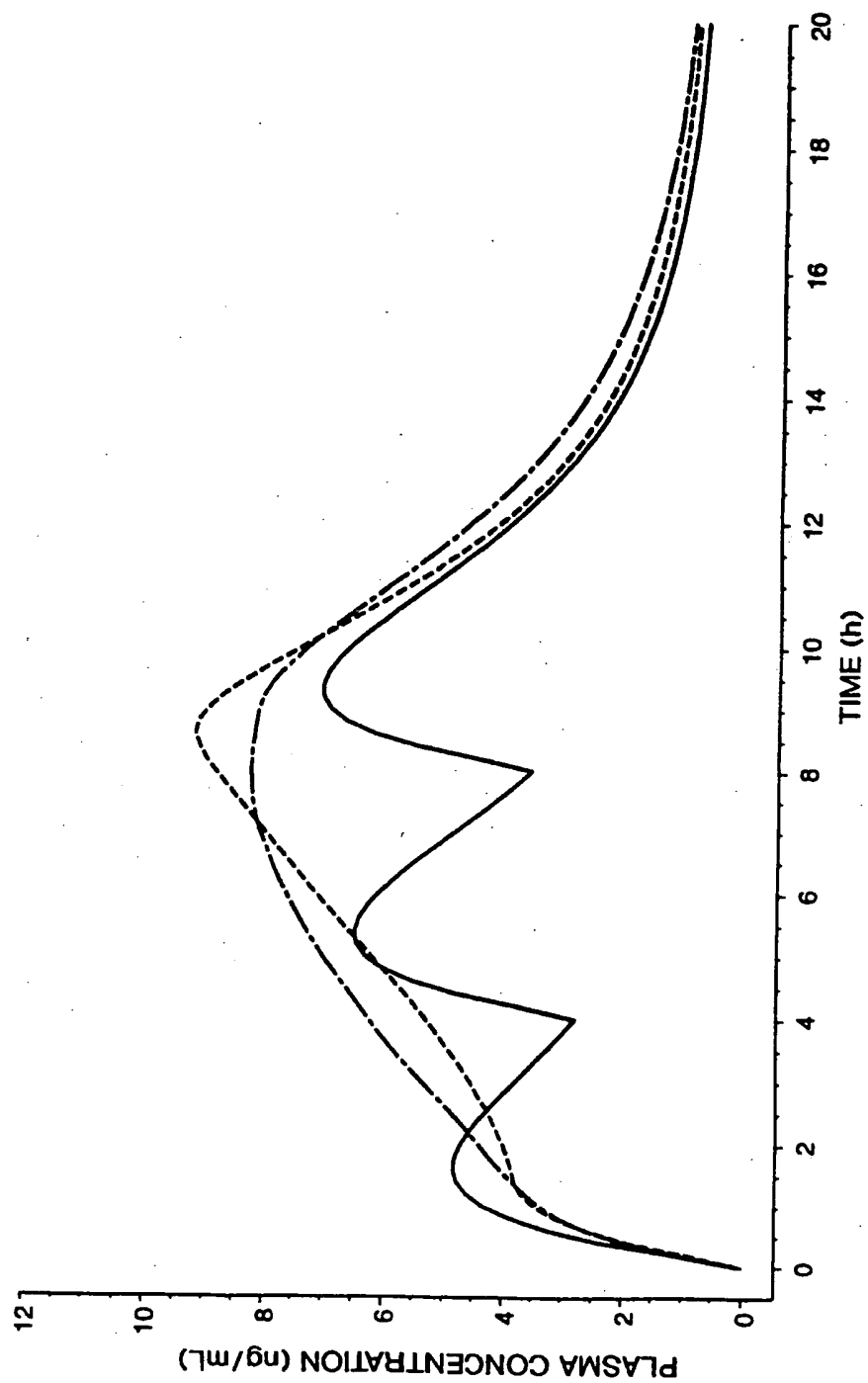


FIG. 10

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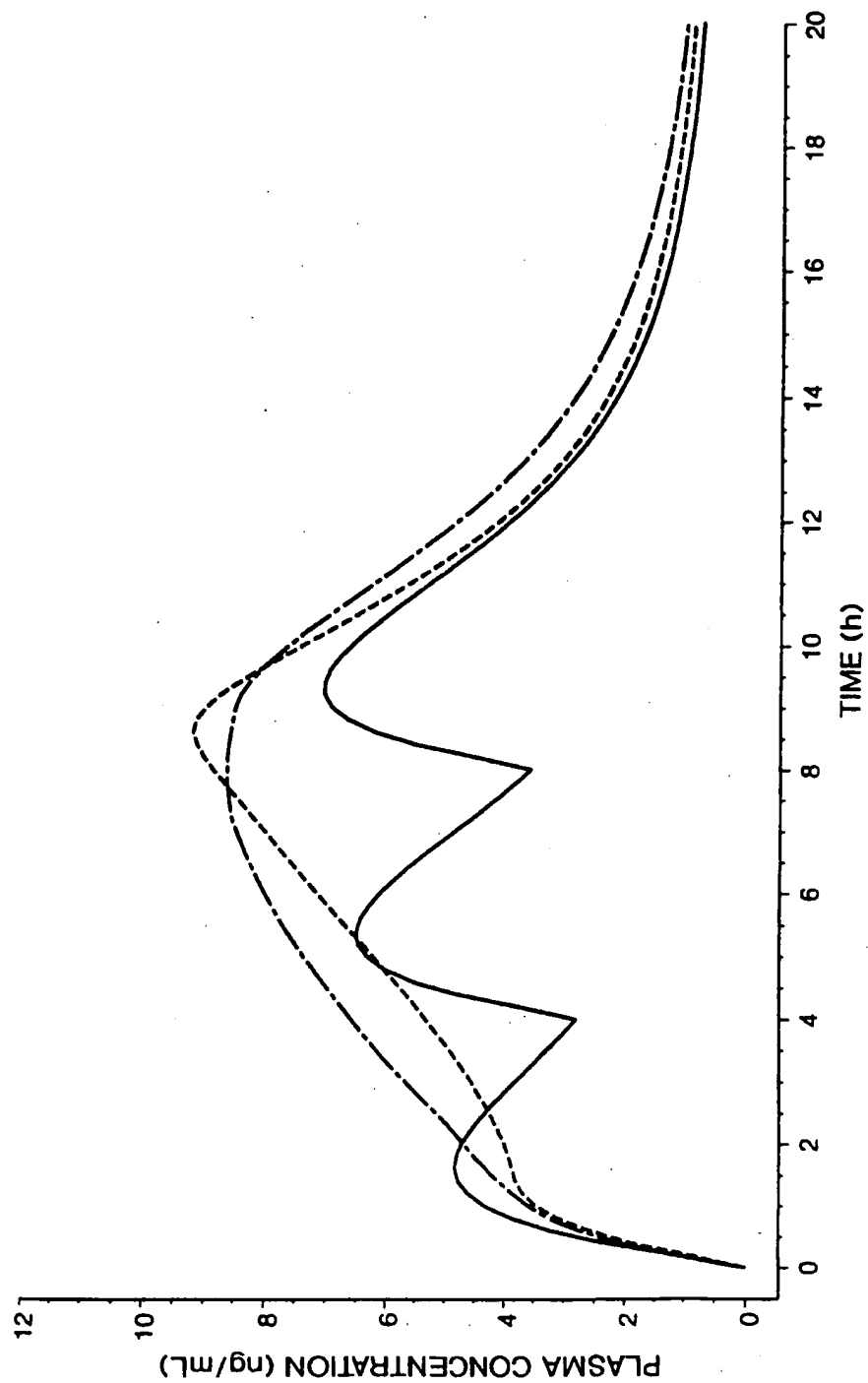


FIG. 11

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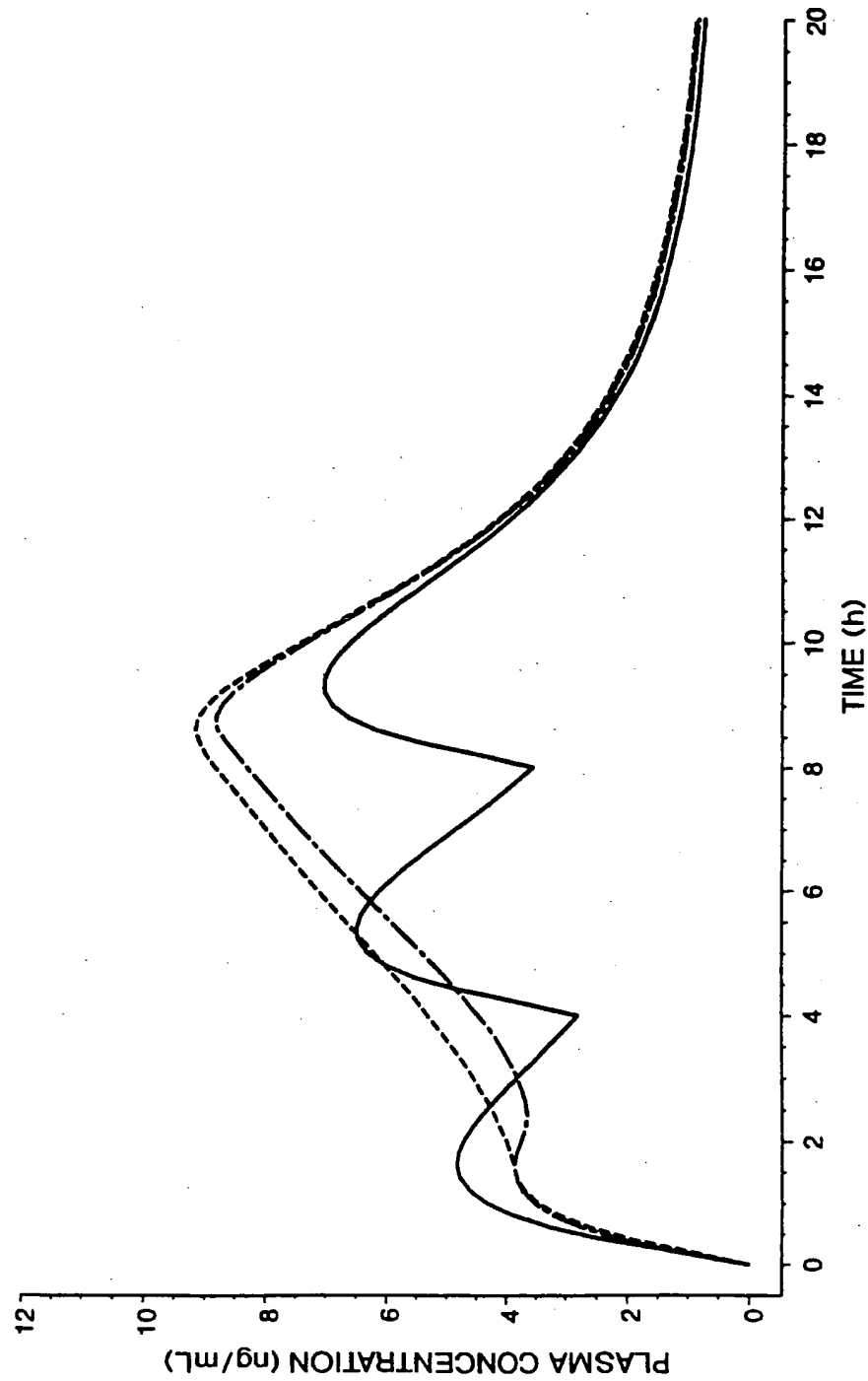


FIG. 12

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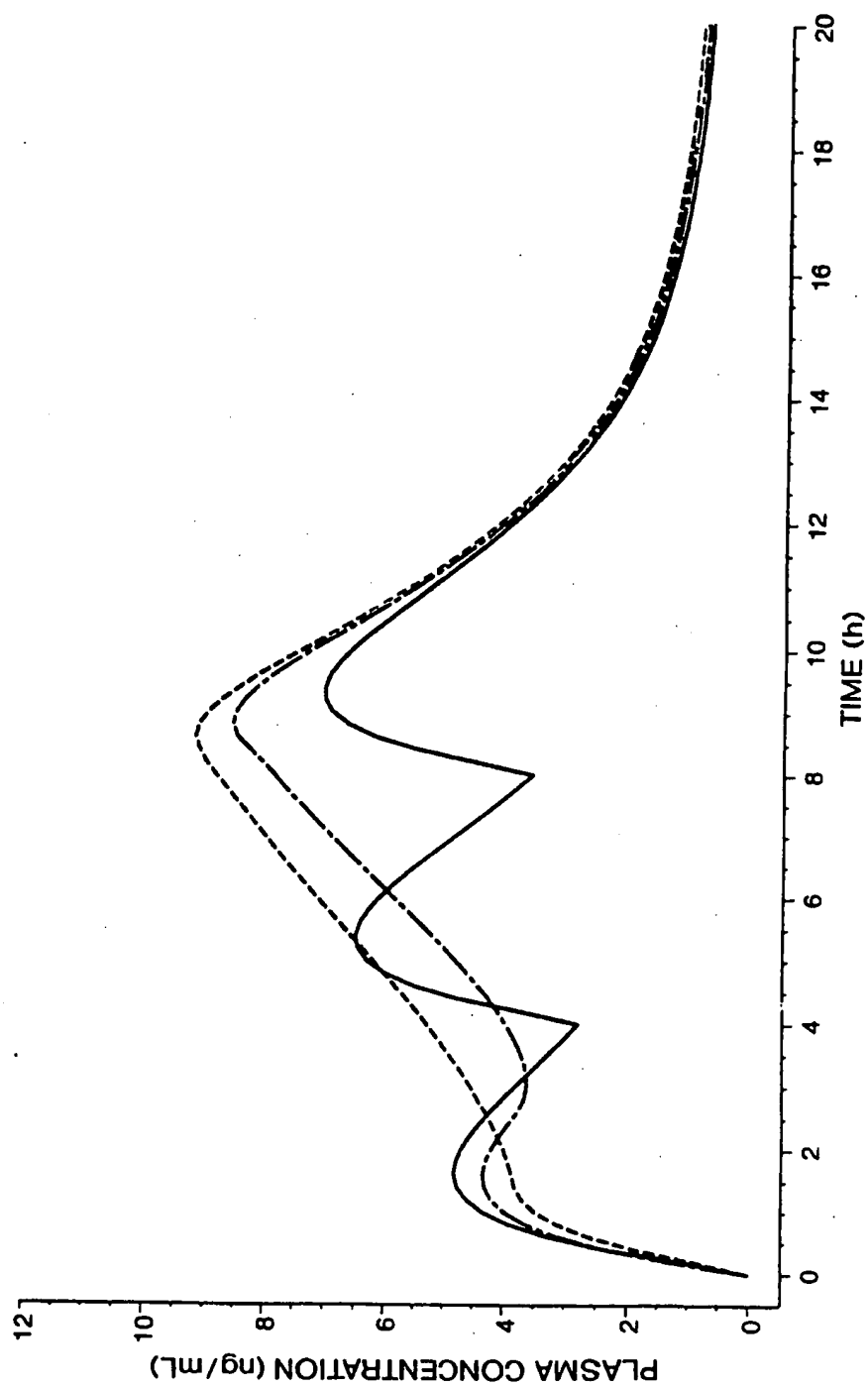


FIG. 13

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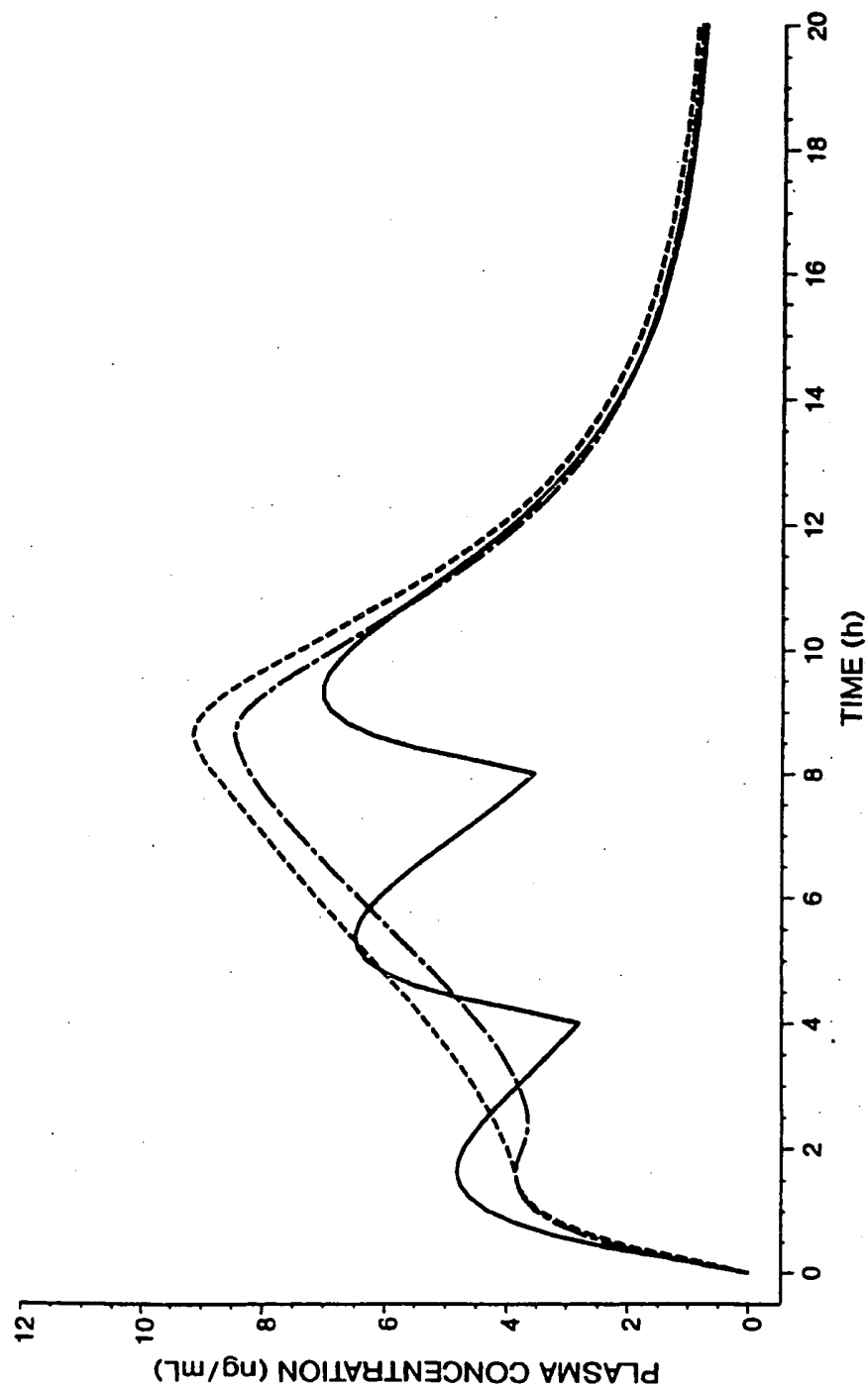


FIG. 14



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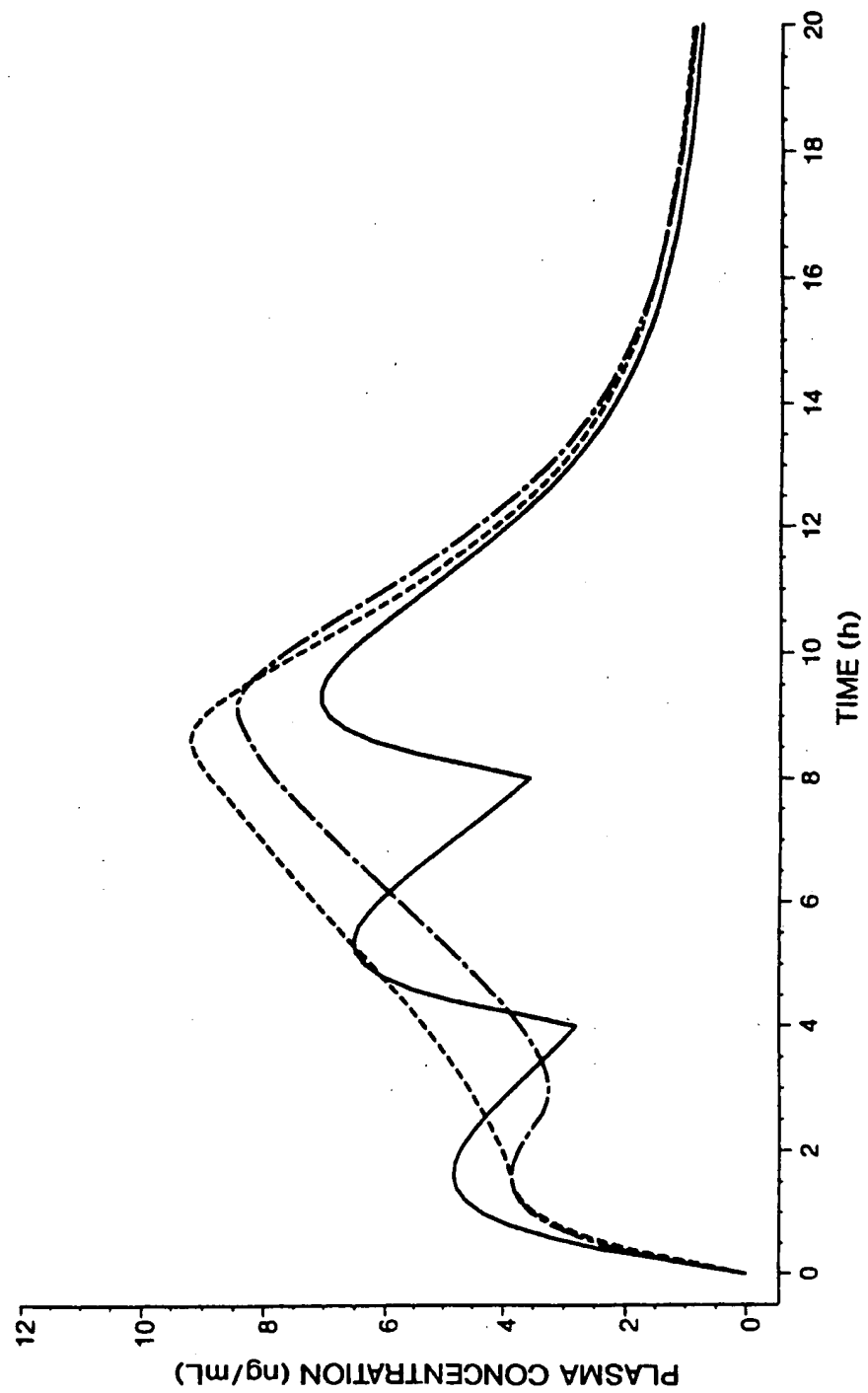


FIG. 15

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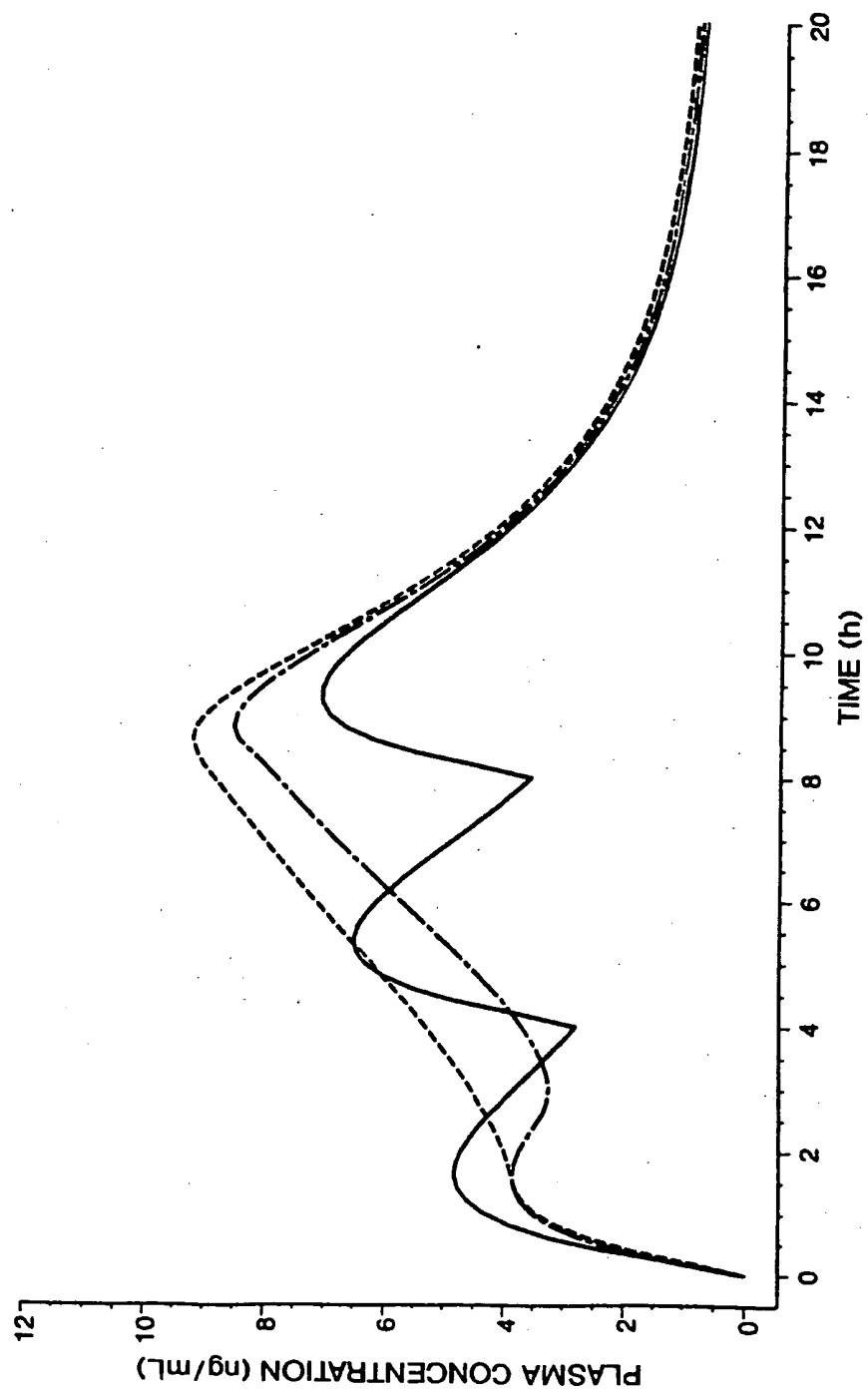
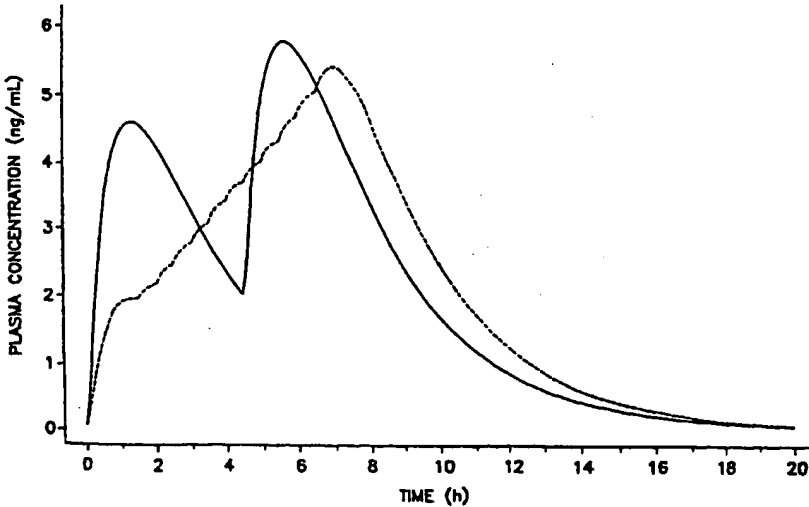


FIG. 16



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(54) Title: DOSAGE FORM PROVIDING A SUSTAINED AND ASCENDING DRUG RELEASE			
			
(57) Abstract <p>A dosage form and a method are disclosed and claimed for administering a drug in a sustained and constantly ascending rate per unit time to provide an intended therapeutic effect while concomitantly lessening the development of unwanted effects.</p>			

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 97/16599

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/50 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Int. Application No.

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